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Declaration under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: METHOD FOR SCREENING FOR COMPOUNDS AS POTENTIAL SEDATIVES OR ANXIOLYTICS

(57) Abstract: The present invention relates to a method for screening a chemical compound for its potential as a sedative or anxiolytica. The invention also relates to a drug development method and to the use of a compound as identified by the screening method for the treatment, prevention or alleviation of anxiety, for inducing. anaesthesia, pre-anaesthesia, muscle relaxation, or sedation, or for treatment, prevention or alleviation of fever cramps or status epilepticus in a subject.

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METHOD FOR SCREENING FOR COMPOUNDS AS POTENTIAL SEDATIVES OR ANXIOLYTICS

The present invention relates to a method for screening a chemical compound for its potential as a sedative or anxiolytica. The invention also relates to a drug development method and to the use of a compound as identified by the screening method for the treatment, prevention or alleviation of anxiety, for inducing anaesthesia, pre-anaesthesia, muscle relaxation, or sedation, or for treatment, prevention or alleviation of fever cramps or status epilepticus in a subject.

BACKGROUND ART

GABA is the major inhibitory neurotransmitter in the mammalian brain and the $GABA_A$ receptor is the site of action of benzodiazepines. Multiple isoforms of $GABA_A$ receptor exist; each receptor comprises a pentameric complex formed by co-assembly of subunits selected from 16 genes (α_{1-6}, β_{1-3}, γ_{1-3}, δ, ε, π, and θ) creating a chloride ion-channel.

The most abundant $GABA_A$ receptor in the mammalian brain comprises α, β, and γ subunits, and the classical anxiolytic benzodiazepines bind to these receptors if they contain $\alpha_{1,2,3 \text{ or } 5}$ and γ_2 subunits. Because the subtypes are differently expressed in the brain as well as in other organs and because different subtypes are considered to be involved in different function, subtype specific compounds have been developed both with agonistic, antagonistic and inverse agonistic potentials. An example of such a subtype specific compound is the non-anxiolytic imidazopyridine zolpidem, which is highly selective for α_1 containing $GABA_A$ receptors and is used as a short acting sedative in humans. α_2, α_3, and α_5 benzodiazepines sites are considered to be involved in anxiolytic properties and similar attempts have been made develop specific compounds for these sites. Such an example is the compound L-838,417, which is a selective α_2, α_3, and α_5 agonist [McKernan et al., Nat. Neurosci. 2000 June; 3(6); 587-92].

In order to develop new subtype specific compounds and to assess their efficacy *in vivo*, it is necessary to test new chemical entities (NCE's) in living animals. As the site of action is in the brain, behavioural testing is essential to determine pharmacokinetic and other ADME properties of the NCE. Furthermore, it is essential to determine the efficacy in terms of hypnotic, sedative, anxiolytic, muscle relaxant, and anticonvulsive properties. Behavioural analyses in animals involve a number of so-called anxiety models, which detect the subjects' capability to take risks. The major problem with these models is that they are only partly predictive to assess a full behavioural response to a NCE with *in vitro* effect on the $GABA_A$ receptor. There

exists no *in vivo* prediction of alpha selectivity. Furthermore, because some of these compounds are sedative, it is hard to determine if their lack of action is specific or linked to its sedative properties. A method that activates systems in the brain relevant for the action of subtype specificity of NCE is therefore badly needed.

The hypothalamo-pituitary-adrenal (HPA) axis consists of the hypothalamic corticotrophin releasing factor (CRF) neurons in the medial parvocellular nuclei of the paraventricular nucleus (PVN), the corticotrophs of the anterior pituitary, and the steroid-producing cells in the adrenal cortex. The HPA axis drives the release of circulating corticosteroids in the blood, and is thus a central component of the stress response. The HPA axis is under negative feedback, as increasing concentrations of plasma corticosteroids will inhibit the activity of the HPA axis via specific receptors for glucocorticosteroids. The HPA axis is under influence by other centers in the brain, and thereby it is activated in response to anxiety and fear. Pharmacological intervention can affect either directly on stress-related pathways, on the CRF neurons, or peripherally to affect the inhibitory feedback on the axis.

Diazepam has been shown to slightly stimulate the HPA axis at the level of the hypothalamic corticotrophin releasing factor (CRF) neurons.

SUMMARY OF THE INVENTION

According to the invention it has now been found that activation of the HPA axis is coupled to mediation through the $GABA_A$ receptors comprising α_1-subtypes and thereby coupled to a sedative effect of the compound.

Thus, in a first aspect, the invention relates to a method for screening a chemical compound for its potential as a sedative or anxiolytica, which method comprises the following steps:

a) exposing the compound to a test system; and

b) measuring the effect of the compound on the activity of the HPA axis.

In a second aspect, the invention relates to a drug development method method, which comprises the identification of a compound by the screening method.

In a third aspect, the invention relates to the use of a compound identified in above method.

Other objects of the invention will be apparent to the person skilled in the art from the following detailed description and examples.

DETAILED DISCLOSURE OF THE INVENTION

In a first aspect, the invention provides a method for screening a chemical compound for its potential as a sedative or anxiolytica, which method comprises the following steps:

a) exposing the compound to a test system; and

b) measuring the effect of the compound on the activity of the HPA axis.

In one embodiment, the chemical compound is a $GABA_A$ receptor modulator.

In a further embodiment, the test system is a test animal, and the compound is exposed to the test animal by administration. In a still further embodiment, the test animal is a non-human animal, such as a mammal. In a further embodiment, the test animal is a rodent, such as a mouse or a rat. In a still further embodiment, the test animal is a non-mammalian vertebrate, such as a reptile, bird or fish.

In a further embodiment, the route of administration of the compound is intraperitoneal (i.p.), intraveneous (i.v.), peroral (p.o.) or subcutaneous (s.c.).

In a still further embodiment, the measurement of the activity of the HPA axis is performed by measuring, in a blood sample from the test animal after administration, the level of plasma corticosterone and/or ACTH.

In a still further embodiment, the test system is an explant system, such as hypothalamic explant cultures, for example rat hypothalamic explant cultures.

In a further embodiment, the method for screening comprises the further step of: c1) selecting the compound as a sedative drug candidate if the compound substantially stimulates the HPA axis. In a special embodiment, the substantial stimulation of the HPA axis is at least a 2-fold increase, preferably at least a 3-fold increase, in corticosterone and/or ACTH over vehicle within the first two hours of administration.

In a still further embodiment, the method for screening comprises the further step of: c2) selecting the compound as an anxiolytica drug candidate if the compound has substantially no effect on the HPA axis. In a special embodiment, the substantially no effect on the HPA axis is less than a 50 percent increase, preferably less than a 25 percent increase, in corticosterone and/or ACTH over vehicle within the first two hours of administration.

In a further aspect, invention provides a drug development method, which comprises the identification of a compound according to the above method for screening.

In a still further aspect, the invention provides the use of a compound identified as a sedative drug candidate by the above method for screening or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for inducing anaesthesia, pre-anaesthesia, muscle relaxation, or sedation, or for treatment, prevention or alleviation of fever cramps or status epilepticus in a subject.

In a still further aspect, the invention provides the use of a compound identified as an anxiolytic drug candidate by the above method for screening or a

pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment, prevention or alleviation of anxiety.

In a further aspect, the invention provides a method for the treatment, prevention, or alleviation of anxiety comprising administering to said subject a therapeutically effective amount of a compound identified as a antiolytica by the above method for screening or a pharmaceutically acceptable salt thereof.

In a still further aspect, the invention provides a method for inducing anaesthesia, pre-anaesthesia, muscle relaxation, or sedation, or for treatment, prevention or alleviation of fever cramps or status epilepticus anxiety comprising administering to said subject a therapeutically effective amount of a compound identified as a sedative by the above method for screening or a pharmaceutically acceptable salt thereof.

Measurement of HPA axis activity

A good measure of the activity of the HPA axis (hypothalamus-pituitary-adrenal axis) is a measure of those hormones that are released in response to the activation, i.e. the adrenocorticotrophic hormone (ACTH) and glucocorticoids (such as corticosterone or cortisol). These hormones can easily be measured in the blood, urine and the saliva of the test animal. Furthermore, activation of the CRF neurons in the hypothalamus can be assessed as activity of transcriptional activation in the neurons (Hoffman et al., J Neuroendocriol. 2002 Apr.; 14(4); 259-68).

One example of measuring the activity of the HPA axis is as follows: The animal is treated with the NCE and sacrificed within an hour. As the release of ACTH occurs within an hour after the stimulation of the CRF neurons, animals are sacrificed at t=0, 5, 15, 30 and 60 minutes after administration. Trunk blood is taken, serum separated and levels of ACTH is measured in the serum by specific radioimmunoassay. Similarly, the level of glucocorticosteroids are determined at t=0, 30, 60, and 120 minutes (the response occurs somewhat later than ACTH) using a radioimmunoassay.

Pharmaceutical Compositions

While a chemical compound as identified by the method according to the invention for use in therapy may be administered in the form of the raw chemical compound, it is preferred to introduce the active ingredient, optionally in the form of a physiologically acceptable salt, in a pharmaceutical composition together with one or more adjuvants, excipients, carriers, buffers, diluents, and/or other customary pharmaceutical auxiliaries.

In a preferred embodiment, the invention provides pharmaceutical compositions comprising the chemical compound of the invention, or a pharmaceutically acceptable salt or derivative thereof, together with one or more pharmaceutically acceptable

carriers therefor, and, optionally, other therapeutic and/or prophylactic ingredients, know and used in the art. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not harmful to the recipient thereof.

The pharmaceutical composition of the invention may be administered by any convenient route which suit the desired therapy. Preferred routes of administration include oral administration, in particular in tablet, in capsule, in dragé, in powder, or in liquid form, and parenteral administration, in particular cutaneous, subcutaneous, intramuscular, or intravenous injection. The pharmaceutical composition may be prepared by the skilled person using standard and conventional techniques appropriate to the desired formulation. When desired, compositions adapted to give sustained release of the active ingredient may be employed.

Further details on techniques for formulation and administration may be found in the latest edition of Remington's Pharmaceutical Sciences (Maack Publishing Co., Easton, PA).

BRIEF DESCRIPTION OF THE DRAWING

The present invention is further illustrated by reference to the accompanying drawing, in which:

Fig. 1 shows the effect of increasing doses of zolpidem and L-838,417 on plasma corticosterone levels in mice. The data represent mean ± S.E.M. of 5 mice per group. Significant effect of compound compared to vehicle *$p<0.05$.

Fig. 2 shows the time course of the effect of 10 mg/kg zolpidem on the HPA axis. The rise in plasma ACTH precedes the rise in corticosterone.

The following example will illustrate the invention further, however, it is not to be construed as limiting.

EXAMPLES

Example 1

Measuring the affect on the HPA axis of Zolpidem in mice

Adult male NMRI mice (23-27 g.) were purchased from Møllegaarden (Denmark). The animals were received at the animal facility, and housed 5 per cage under 12:12 light: dark cycle, humidity and temperature controlled room for at least 7 days before the experiment. Food and water were available ad libitum. All procedures were conducted in accordance with the Danish National Guide for Care and Use of Laboratory animals. Zolpidem was purchased from Tocris Ltd (Bristol, UK) and L-

838,417 synthesised according to WO 98/04559 and was injected in a volume of 10 ml/kg and dissolved in 5% Chremophor.

The two drugs were administered (i.p.) at doses 0,025, 1,25, 2.5, 12.5 and 25 mg/kg. The mice were returned to their home cages and sacrificed by decapitation 60 minutes after drug administration and trunk blood was collected in centrifuge tubes containing 2 mg EDTA. Plasma aliquots were stored at –20°C until hormone levels were determined.

Plasma corticosterone was measured directly without prior extraction by a commercially [^{125}I] corticosterone radioimmunoassay kit from Amersham. The experiment was performed twice. The data were analysed by a two-way analysis of variance (ANOVA) followed by the Dunn's test. All data are represented as group means and the standard error of means (SEM).

Zolpidem significantly and dose-dependently increased plasma corticosterone in doses from 0,5 mg/kg. As demonstrated in Fig. 1 the effect reached a maximum at 12.5 mg/kg and not further increased by 25 mg/kg. In contrast, L-838,417 had no effect on corticosterone in doses up to 12.5 mg/kg (Fig. 1). When tested 2 h after administration of 12.5 mg/kg L-838,417 no effects on plasma corticosterone was observed.

CLAIMS:

1. A method for screening a chemical compound for its potential as a sedative or anxiolytica, which method comprises the following steps:
   a) exposing the compound to a test system; and
   b) measuring the effect of the compound on the activity of the HPA axis.

2. The method according to claim 1, wherein the chemical compound is a $GABA_A$ receptor modulator.

3. The method according to claims 1 or 2, wherein the test system is a test animal, such as a mouse or a rat, and the compound is exposed to the test animal by administration.

4. The method according to claim 3, wherein the measurement of the activity of the HPA axis is performed by measuring, in a blood sample from the test animal after administration, the level of plasma corticosterone and/or ACTH.

5. The method according to any one of claims 1-4, comprising the further step:
   c1) selecting the compound as a sedative drug candidate if the compound substantially stimulates the HPA axis.

6. The method according to any one of claims 1-4, comprising the further step:
   c2) selecting the compound as an anxiolytica drug candidate if the compound has substantially no effect on the HPA axis.

7. A drug development method, which comprises the identification of a compound by the method according to any one of the claims 1-6.

8. The use of a compound identified as a sedative drug candidate by the method according to any one of the claims 1-5 or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for inducing anaesthesia, pre-anaesthesia, muscle relaxation, or sedation, or for treatment, prevention or alleviation of fever cramps or status epilepticus in a subject.

9. The use of a compound identified as an anxiolytic drug candidate by the method according to any one of the claims 1-4 and 6 or a pharmaceutically acceptable

salt thereof for the manufacture of a medicament for the treatment, prevention or alleviation of anxiety.

10. A method for the treatment, prevention, or alleviation of anxiety comprising administering to said subject a therapeutically effective amount of a compound identified as a antiolytica by the method according to any one of the claims 1-4 and 6 or a pharmaceutically acceptable salt thereof.

11. A method for inducing anaesthesia, pre-anaesthesia, muscle relaxation, or sedation, or for treatment, prevention or alleviation of fever cramps or status epilepticus anxiety comprising administering to said subject a therapeutically effective amount of a compound identified as a sedative by the method according to any one of the claims 1-5 or a pharmaceutically acceptable salt thereof.

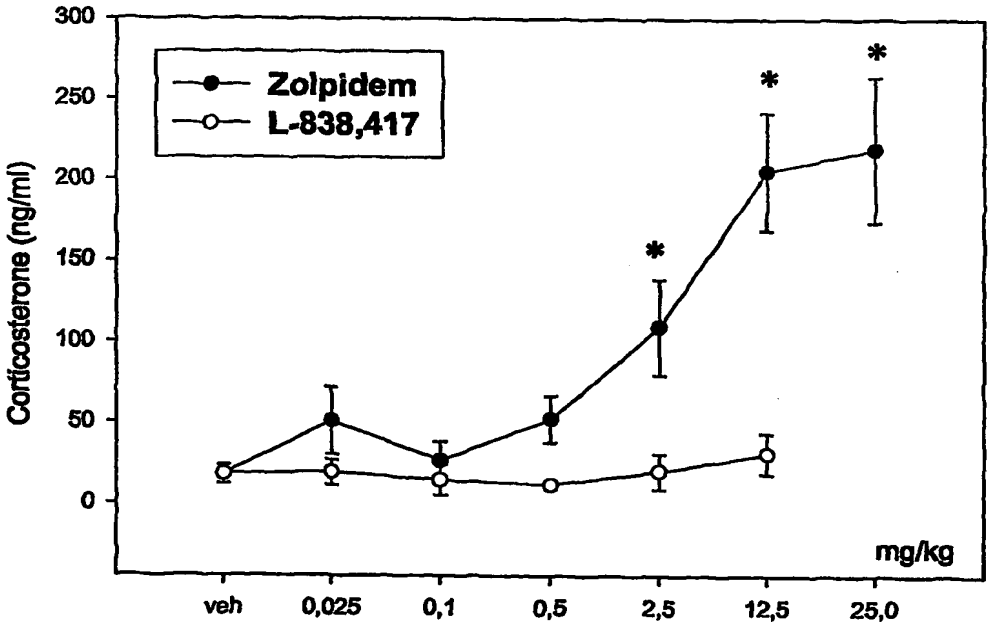
Zolpidem
L-838,417
Corticosterone (ng/ml)
300
250
200
150
100
50
0
mg/kg
veh
0,025
0,1
0,5
2,5
12,5
25,0
*
*
*

Fig. 1

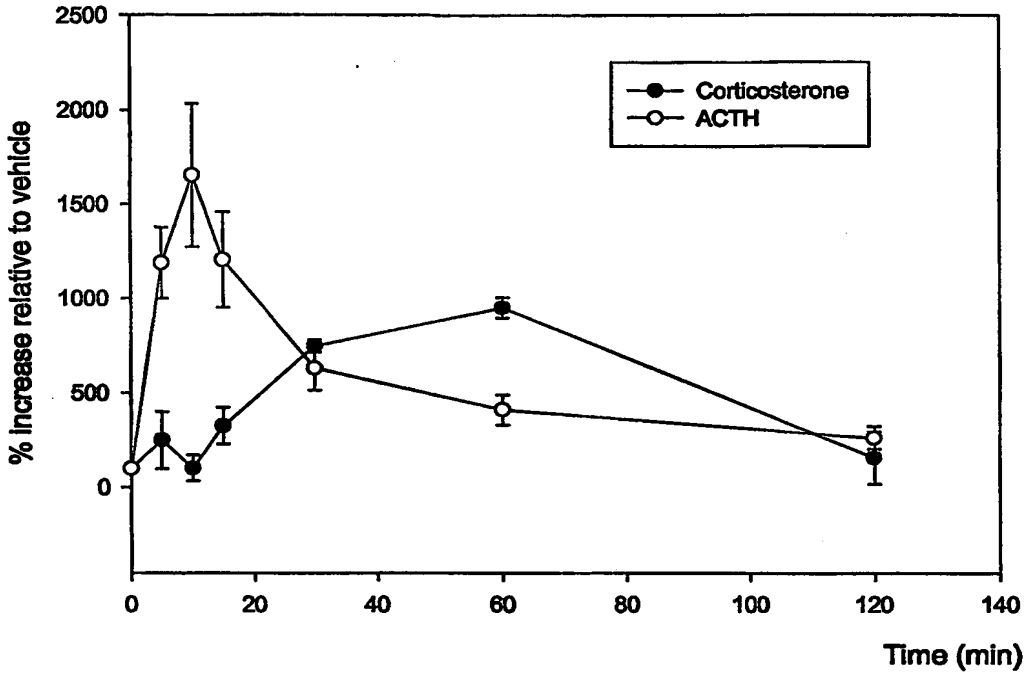
2500
2000
1500
1000
500
0
% increase relative to vehicle
Corticosterone
ACTH
0
20
40
60
80
100
120
140
Time (min)

Fig. 2

INTERNATIONAL SEARCH REPORT

International Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 G01N33/74 A61K31/00 A61K31/437 A61K31/519 G01N33/94
G01N33/50

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 G01N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, BIOSIS, EMBASE, MEDLINE, EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01/05222 A (RES DEV FOUNDATION) 25 January 2001 (2001-01-25) claims 12,13	1,3,4
X	WO 02/40700 A (RES DEV FOUNDATION) 23 May 2002 (2002-05-23) claims 12,13	1,3,4
X	CRESTANI FLORENCE ET AL: "Mechanism of action of the hypnotic zolpidem in vivo" BRITISH JOURNAL OF PHARMACOLOGY, vol. 131, no. 7, December 2000 (2000-12), pages 1251-1254, XP001189786 ISSN: 0007-1188 abstract	8,11

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 April 2004	13/05/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	van der Kooij, M

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/50860

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MCKERNAN R M ET AL: "Sedative but not anxiolytic properties of benzodiazepines are mediated by the GABAA receptor alpha1 subtype" NATURE NEUROSCIENCE, vol. 3, no. 6, June 2000 (2000-06), pages 587-592, XP002277202 ISSN: 1097-6256 cited in the application abstract page 589, column 2, paragraph 2 -page 599, column 2, paragraph 1	9,10
X	WO 00/44752 A (MERCK SHARP & DOHME ;MOORE KEVIN WILLIAM (GB); CARLING WILLIAM ROB) 3 August 2000 (2000-08-03) page 8, line 6 - line 14 claims 1,4,9,13,15	9,10
A	KRALIC J E ET AL: "DELETION OF GABAA RECEPTOR (GABAA - R) alpha1 SUBUNIT ALTERS BENZODIAZEPINE (BZD) SITE PHARMACOLOGY, FUNCTION AND RELATED BEHAVIOR." SOCIETY FOR NEUROSCIENCE ABSTRACT VIEWER AND ITINERARY PLANNER, vol. 2002, 2002, page Abstract No. 39.12 XP001189785 32nd Annual Meeting of the Society for Neuroscience;Orlando, Florida, USA; November 02-07, 2002 abstract	1-11
A	STAHL STEPHEN M: "Selective actions on sleep or anxiety by exploiting GABA-A/benzodiazepine receptor subtypes" JOURNAL OF CLINICAL PSYCHIATRY, vol. 63, no. 3, March 2002 (2002-03), pages 179-180, XP008029821 ISSN: 0160-6689 the whole document	1-11
A	BARBACCIA M L ET AL: "Stress and neurosteroids in adult and aged rats." EXPERIMENTAL GERONTOLOGY. ENGLAND 1998 NOV-DEC, vol. 33, no. 7-8, November 1998 (1998-11), pages 697-712, XP001189793 ISSN: 0531-5565 abstract page 698, paragraph 1	1-11

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/50860

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CULLINAN WILLIAM E: "GABAA receptor subunit expression within hypophysiotropic CRH neurons: A dual hybridization histochemical study" JOURNAL OF COMPARATIVE NEUROLOGY, vol. 419, no. 3, 10 April 2000 (2000-04-10), pages 344-351, XP008029812 ISSN: 0021-9967 abstract	1-11

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims 8 and 9 encompass a genus of compounds defined only by their function wherein the relationship between the structural features of the members of the genus and said function have not been defined. In the absence of such a relationship either disclosed in the as-filed application or which would have been recognized based upon information readily available to one skilled in the art, the skilled artisan would not know how to make and use compounds that lack structural definition. The fact that one could have assayed a compound of interest using the claimed assays does not overcome this defect since one would have no knowledge beforehand as to whether or not any given compound (other than those that might be particularly disclosed in an application) would fall within the scope of what is claimed. It would require undue experimentation (be an undue burden) to randomly screen undefined compounds for the claimed activity (Art. 83 and Art. 84 EPC). Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to zoldipem and L-838,417 (see example 1 on page 5-6) in relation for inducing anaesthesia, pre-anaesthesia, muscle relaxation, or sedation or for treating, preventing or alleviating fever cramps or status epilepticus (claim 8) or for treating, preventing or alleviating anxiety (claim 9).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/50860

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 10 and 11 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: -
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 03/50860

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 0105222	A	25-01-2001	AU	6216700 A	05-02-2001
			CA	2375943 A1	25-01-2001
			CN	1371243 T	25-09-2002
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